Vancomycin & New Agents for MRSA Infections

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The Changing Face of S. aureus: The 1940’s to Present

S. aureus
- Penicillin sensitive
- Penicillin resistant
- Methicillin (Oxacillin) resistant (MRSA or ORSA)
  - Traditional hospital acquired (HA-MRSA)
- Vancomycin intermediate (VISA/GISA)
- Vancomycin resistant (VRSA)
- Heterovariants (h-VISA)
- Agr II status (+ dysfunctional)
- Community acquired (CA-MRSA)
- Tolerance
MRSA Treatment Options

Currently Available Options

- Vancomycin
- Clindamycin
- TMP/SMX
- Doxycycline/Minocycline
- Quinupristin/Dalfopristin
- Linezolid
- Daptomycin
- Tigecycline
- Telavancin (Approvable Letter from FDA)
- Delbavancin (Approvable Letter from FDA)

Vancomycin Clinical Performance

- Apparently vancomycin has been under performing & needs a “fix”
  - Under dosed
    - Treatment guidelines recommend increasing troughs from 5-10 mg/L to 10-20 mg/L
  - Susceptibility over reported
    - Change in CLSI breakpoints January 2006
    - Environmental factors
      - Inoculum size
      - Aerobic vs anaerobic environment
# Vancomycin Treatment Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Organ</th>
<th>Dose</th>
<th>Trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP/VAP</td>
<td>ATS/IDSA</td>
<td>15 mg/KgQ12H</td>
<td>15-20</td>
</tr>
<tr>
<td>Meningitis</td>
<td>IDSA</td>
<td>15 mg/Kg Q8 or 12H</td>
<td>15-20*</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>BSAC</td>
<td>1GmQ12H</td>
<td>10-15</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>AHA</td>
<td>15 mg/KgQ12H</td>
<td>10-15*</td>
</tr>
</tbody>
</table>

*Graded Recommendation

• No evidence offered that:
  - Initial dose will produce desired troughs
  - That higher troughs are more effective
  - That higher troughs are safe

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**IDSA Lecture**

Point: Vancomycin Is Not Obsolete for the Treatment of Infection Caused by Methillin-Resistant *Staphylococcus aureus*

Julie E. Mofz and Edmund E. Murray,
Department of Internal Medicine, Division of Infectious Diseases and Center for Emerging and Reemerging Pathogens, and Department of Microbiology and Molecular Genetics, University of Texas Health Science Center at Houston

Counterpoint: Vancomycin and *Staphylococcus aureus*—An Antibiotic Enters Obsolescence

Drs. Brandeis and Califf
Division of Infectious Disease and Geographic Medicine, Department of Medicine, Stanford University, Stanford, and Division of Infectious Disease, Santa Clara Valley Medical Center, San Jose, California

Clin Infect Dis 44:12 (June 15, 2007)
Factors Affecting Vancomycin Clinical Performance

- Poor tissue penetration
- Bactericidal but a slow killer of gram positive pathogens
- Level of glycocalyx production
- Limited to no affect on toxin production
- Lysis of cell wall could aid toxin release
- High bacterial inoculum
- Anaerobic conditions

*S aureus #29213 vs Vancomycin Under Aerobic Conditions*

Vancomycin Pharmacokinetics
CID 2006:42 (Suppl 1), S35.

Log Serum Concentration

\[ C = Ae^{-\alpha t} + Be^{-\beta t} \]

Infusion, Distribution \( \alpha \), & Elimination \( \beta \)

Central Compartment

Peripheral Compartment

\( K_0 \)

\( V_C \)

\( K_{12} \)

\( K_{21} \)

\( K_{el} \)

Time

Vancomycin Pharmacodynamics:
Which Parameter ? & What Quantitative Value ?

Change in Log _{10} cfu/Thigh Over 24 H

Ebert, S. ICAAC #439, 1987
## Vancomycin AUC/MIC Ratio

<table>
<thead>
<tr>
<th>Source</th>
<th>AUC/MIC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional dosing*</td>
<td>Total ~400 &amp; Unbound 100-250</td>
</tr>
<tr>
<td>Moise Am J Health Syst Pharm 2000</td>
<td>Total 345 (clinical) &amp; 850 (microbiologic)</td>
</tr>
<tr>
<td>Craig ICAAC A644 2006</td>
<td>500**</td>
</tr>
<tr>
<td>Dudley ICAAC 2031, 1999</td>
<td>86-460 for 50% Killing</td>
</tr>
</tbody>
</table>

*Vancomycin 1 Gm Q12H & Pathogen MIC = 1 mg/L
**Inoculum size and MIC Dependent (Murine Thigh Model)

### Susceptible S. aureus vs. GISA

Intensive Care Med 2007

Daily doses on the probability of attaining $\text{AUC}_{24h}/\text{MIC} \geq 400$
# Median Duration of Bacteremia & Fever in MRSA Endocarditis

*Adapted: Levine Ann Intern Med 115:574, 1991*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median Duration Bacteremia (Days)</th>
<th>Median Duration Fever (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>42</td>
<td>9 (6-11)</td>
<td>7 (4-9)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>22</td>
<td>7 (5-11)</td>
<td>7 (3-8)</td>
</tr>
<tr>
<td>Vanc/Rifampin</td>
<td>20</td>
<td>9 (6-13)</td>
<td>7 (3-10)</td>
</tr>
<tr>
<td>Left Sided</td>
<td>8</td>
<td>9 (3-10)</td>
<td>7 (N/A)</td>
</tr>
<tr>
<td>Right Sided</td>
<td>34</td>
<td>7 (5-11)</td>
<td>8 (3-10)</td>
</tr>
</tbody>
</table>

(95% CI)

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## Vancomycin MIC versus eradication rates

<table>
<thead>
<tr>
<th>Vancomycin (µg/ml)</th>
<th>No. of Isolates</th>
<th>Median DTE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median Duration of Vancomycin Therapy (days)</th>
<th>Eradication Rate by EOT&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Median Reduction in log_{10} CFU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>13</td>
<td>6.0</td>
<td>13.0</td>
<td>10/13 (77)</td>
<td>3.06</td>
</tr>
<tr>
<td>1.0</td>
<td>7</td>
<td>9.5</td>
<td>17.0</td>
<td>5/7 (71)</td>
<td>3.09</td>
</tr>
<tr>
<td>2.0</td>
<td>14</td>
<td>&gt; 15.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18.5</td>
<td>3/14 (21)</td>
<td>2.75</td>
</tr>
</tbody>
</table>

<sup>a</sup>DTE, day to eradication.

<sup>b</sup>EOT, end of treatment.

<sup>c</sup>The median time to eradication is >15 days, as only 21% of patients showed clearance of bacteremia.

Moise, PA et al AAC 51(7): 2582-2586, 2007
Factors Affecting Vancomycin Clinical Performance

- Heteroresistance (~2 to 11%)
- GISA/VISA or VRSA
- Micro-colony variants
- Agr polymorphism
- Tolerance (~15% for wild type MRSA)
  - Loss of bactericidal activity
- Vancomycin MIC value
  - Inoculum size
  - Anaerobic conditions
  - Geographic variability
  - Testing Method

Vancomycin Susceptibility S. aureus

CLSI 2006

- Sensitive (VSSA)
  - Vancomycin MIC ≤ 2 mg/L
- Heteroresistant strain (h-VISA)
  - Vancomycin MIC = 1-2 mg/L (Still CLSI Sensitive)
- Intermediate (VISA or GISA)
  - Vancomycin MIC = 4-8 mg/L
- Resistant (VRSA)
  - Vancomycin MIC > 16 mg/L
    - Lab needs to backup primary testing with 6mg/L vancomycin overnight plate
- Tolerance (MBC / MIC > 16-32)
Clinical Laboratory Support

Many hospitals still report out susceptibility as sensitive (S), intermediate (I), or resistant (R)
Automated MIC testing may not report an actual MIC value unless the MIC > 1 mg/L
Labs do not test for heteroresistance or routinely perform MBC’s
Vancomycin levels
  1. Patient usually must be at steady state
  2. Whole process in itself consumes 24-48 hours
  3. Trial and error dosing adjustment
  4. Time to Target attainment where trough 10 – 20 mg/L

Tolerance to Vancomycin at MD Anderson Cancer Center

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>0.25</td>
<td>4.0</td>
</tr>
<tr>
<td>MRSE</td>
<td>0.25</td>
<td>4.0</td>
</tr>
<tr>
<td>Staph. <em>hemolyticus</em></td>
<td>1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Strep. <em>viridans</em></td>
<td>0.12</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Linezolid Activity Compared Other Agents in 2006
LEADER Surveillance Program (USA) 5,374 Strains

<table>
<thead>
<tr>
<th>Pathogen (No. Tested/ Antimicrobial Agent)</th>
<th>MIC (µg/ml) 50%</th>
<th>90%</th>
<th>Range</th>
<th>% By Category Suscept/Resist</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (2,913)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>2</td>
<td>0.25-8</td>
<td>&gt; 99.9 / -</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≤ 0.25</td>
<td>&gt; 2</td>
<td>≤0.25-2</td>
<td>75.0 / 24.8</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.25</td>
<td>0.5</td>
<td>≤0.06-2</td>
<td>99.9 / -</td>
</tr>
<tr>
<td>Oxacillin⁶</td>
<td>&gt; 2</td>
<td>&gt; 2</td>
<td>≤0.25-2</td>
<td>43.4 / 56.6</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>0.5</td>
<td>0.5</td>
<td>≤0.25-2</td>
<td>99.9 / 0.0</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2-8</td>
<td>100.0 / 0.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤ 2</td>
<td>≤ 2</td>
<td>≤ 2-8</td>
<td>94.0 / 5.5</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>≤ 0.5</td>
<td>≤ 0.5</td>
<td>≤ 0.5-2</td>
<td>97.3 / 2.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>1</td>
<td>0.25-4</td>
<td>99.9 / 0.0</td>
</tr>
</tbody>
</table>

CLSI 2007

Relationship of MIC & Bactericidal Activity to Efficacy of Vancomycin for the Treatment of MRSA Bacteremia
Sakoulas, G et al J Clin Micr 42:2398-2402, 2004

- If MRSA MIC < 0.5 mg/L
  - 55.6% successful outcome
- If MIC 1 or 2 mg/L
  - 9.5% successful outcome
- High vancomycin MIC’s may increase risk of resistance to newer agents (i.e. Daptomycin)
Vancomycin trough concentrations (mcg/ml) vs Hospital Mortality

Calculated
Area Under the Concentration Curve (mcg.h/ml)

Jeffres, MN et al Chest 130:947-955, 2006
Clinical Response Based on Targeted Trough (Goal = Unbound Trough Concentration $\geq 4 \times$ MIC)

Hidayat, LK et al Arch Intern Med 166:2138-2144, 2006

Vancomycin Nephrotoxicity

<table>
<thead>
<tr>
<th></th>
<th>$C_{p_{min}} &lt; 15 \text{ mg/L}$</th>
<th>$C_{p_{min}} &gt; 15 \text{ mg/L}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jeffres</strong> K789 ICAAC 2006</td>
<td>30.2%</td>
<td>58.8%</td>
</tr>
<tr>
<td><strong>Such</strong> L1298 ICAAC 2006</td>
<td>0.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td><strong>Hidayat</strong> Arch Intern Med 2006</td>
<td>0.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td><strong>Nguyen</strong> K1096 ICAAC 2007</td>
<td>6.2%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>
Getting it Right the First Time without Delay: What the Lab is Not Telling You

**Variables**

1. CA-MRSA vs HA-MRSA
2. MIC value
   - Timing not apriori & formatting of data not helpful
3. Heteroresistant strain (≤11%)
4. Tolerant strain (15%)
5. Glycocalyx
6. Agr status
7. Vancomycin level
   - Steady state level will take 24-48 hrs then trial & error dosing

**Threshold for change?**
Will higher trough concentrations improve vancomycin performance?

- Current data suggests higher troughs do not improve efficacy & may be more nephrotoxic
- Success use of vancomycin may be tied to the MIC, agr status, & tolerance
- Much of the needed clinical data is not being provided by most hospital laboratories
- So far, difficult to establish new agents as statistically better than vancomycin

Suggested First Line Agents for CA-MRSA S/STI
IDSA Guidelines 41:1373-1830, 2005

- Clindamycin (D-test to screen for inducible resistance)
  4 300-450 mg 3 times per day oral
- TMP/SMX (Does not cover Group A Streptococcus)
  4 DS tab (160mg/800mg) Q12H X 10-14 days oral
- Minocycline or Doxycycline (21% failure rates reported)
  4 100mg Q12H X 10-14 days oral
- Adjunct Therapy
  4 4% Chlorhexidine gluconate wash Q24H X 5 days
  4 2% Calcium Mupirocin 1Gm single use tube Q12H X 10 days
Community Acquired MRSA (CA-MRSA)

4 Background
- Influenza common preceding CA-MRSA or concomitant
- Gram positive cocci in groups on gram stain
- X-ray has cavitary infiltrates + multiple lobes
- CA-MRSA prolific toxin producer & can kill quickly

4 Treatment (No preference)
- Vancomycin
  - Possible issues with lung penetration, slow kill rate, failure to shut down toxin production, & cell lysis upon death
- Linezolid
  - Note:
    - Recommendations for pneumonia different than S/STI
    - Daptomycin cannot be used for pneumonia

Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)

Clinical cure (%)
(excluding missing and indeterminate)

- Linezolid: 45.4, 48.9, 62.2
- Vancomycin: 36.1, 45.2, 59.2

P values:
- Linezolid vs Vancomycin: 0.07, 0.06, 0.001

MRSA: 45.4 vs 36.1 (P=0.07), 48.9 vs 45.2 (P=0.06), 62.2 vs 59.2 (P=0.001)
MRSA Treatment Options

Investigational agents when approved will likely have complicated skin infection as only FDA approved indication

- Oritavancin (Targenta)
- Ceftobiprole
- Ceftaroline
- Iclaprim (Arpida)

New Agents

Where should these new drugs be used

- VRE
- When MRSA Vancomycin MIC > 1 mg/L
  - Automated testing may under estimate MIC value
  - Difficult to call if lab reports out MIC < 1 mg/L or S,I, or R
- Empiric therapy for HAP / VAP
  - Exception Daptomycin which binds to surfactant

Where not to use the drug

- First line agent MSSA or VSE
- First line therapy for CA-MRSA
  - Possible exception pneumonia
Conclusions

- Tremendous diversity in what we call staphylococci today
- Decision to use vancomycin is complicated & at minimum probably requires a MIC
- Concerns about the future utility of vancomycin as a first line agent
- Been difficult to establish new agents as superior to vancomycin
  4 Pharmacoeconomic arguments favor new agents